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Brain training with neurofeedback in patients with mild cognitive impairment: a review study

Entrenamiento cerebral con neurofeedback en pacientes con deterioro cognitivo leve: un estudio de revisión

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SUMMARY

Objective: *The study aimed to review the efficacy of Neurofeedback training in patients with Mild Cognitive Impairment (MCI).*

Method: *Review in scientific databases Science Direct, Web of Science (WoS)-ISI of Thompson Reuters-, Scopus, and PubMed. Taking as reference key terms in the English language: "mild cognitive impairment", "mild cognitive decline", "Neurofeedback", "Brain ware" and "EEG feedback.*

Results: *Most studies were published between 2019 and 2020. No homogeneity was found in the protocols used in terms of training time, EEG frequency band stimulation, age groups, sample size, and gender. Unanimity was found in the efficacy of Neurofeedback training on physiological and cognitive performance in patients with MCI.*

Conclusions: *Neurofeedback stimulation has proven to be an effective tool for the rehabilitation of cognitive functions and physiological activity in patients with MCI.*

Keywords: *Neurofeedback, mild cognitive impairment, cognitive processes, functional connectivity.*

RESUMEN

Objetivo: *El objetivo del estudio fue la revisión sobre la eficacia del entrenamiento con Neurofeedback en pacientes con Deterioro Cognitivo Leve (DCL).*

Método: *Revisión en bases de datos científicas Science Direct, Web of Science (WoS)-ISI-de la Thompson Reuters-, Scopus, y PubMed. Tomando como referencia términos claves en el idioma inglés: "mild cognitive impairment", "mild cognitive decline", "Neurofeedback", "Brain ware" y "EEG feedback. Resultados: La mayoría de los estudios fueron publicados entre los años 2019 y 2020. No se encontró homogeneidad en los protocolos utilizados en términos de tiempo de entrenamiento, estimulación de banda de frecuencia de EEG, grupos etarios, tamaño de la muestra y género. Se encontró unanimidad en la eficacia del entrenamiento con Neurofeedback sobre el rendimiento fisiológico y cognitivo en pacientes con DCL.*

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Conclusiones: *La estimulación a través de Neurofeedback, ha demostrado ser una herramienta eficaz para la rehabilitación de funciones cognitivas y actividad fisiológica en pacientes con DCL.*

Palabras clave: *Neurofeedback, deterioro cognitivo leve, procesos cognitivos, conectividad funcional*.

INTRODUCTION

Use of neurofeedback as an intervention method

The first studies related to the stimulation of non-invasive brain activity were carried out in animals, at the University of California (USA), by exploring the brain waves of the Alpha (α) rhythm, linked to the stages of relaxation (1). Since the late 1960s and early 1970s, human trials were conducted, mainly in individuals with pharmacologically resistant epilepsy, suggesting that it was possible to recondition brain wave patterns for a specific purpose (2).

The use of Neurofeedback (NF) is based on neurofeedback principles and is a neurobehavioral technique that makes it a non-invasive and non-pharmacological treatment option. It has gained interest and clinical relevance in multiple pathologies (3). It monitors electrical activity through a computer-brain interface, which allows the subject to control and modify their own brain activity, based on feedback and conditioning principles (4), which allows the subject, based on their capacity for learning and conditioning, voluntarily change their dynamic rhythms (5).

Neurofeedback is usually established from measurements of frequency, location, amplitude, and/or duration of brain electrical activity and is carried out through specific stimuli, these being the direct correlate of the biological signal to be regulated (6). Therefore, these fluctuations are not random but depend on the specific task and the determined cognitive configuration (7). If adequate feedback is generated with repeated training, changes in brain activity and, in turn, its projection in human cognition would occur (8).

To adequately achieve this feedback, first the parameter to be modified is chosen: amplitude of the oscillations and/or frequency band, and a specific task and the stimulus to be used are assigned. Thus, when the parameter exceeds the predefined threshold, the subjects are provided with a sensory reward that permeates the transformation, based on operant conditioning and biofeedback (9,11,12).

Training of Cognitive Functions through Neurofeedback

The recording and processing of neural activity, through EEG, is one of the first objective measures used to study brain functionality (13); specifically, the so-called "mental states" (14). This is achieved by trying to correlate these cognitive domains with the different frequency bands identified through Fourier analysis and precisely defined (10).

Each representation of brain activity is associated with a distribution of EEG band values (5), which are produced by ionic flow from large groups of dendrites that are recorded in cerebral cortex currents in certain groups of neurons, due to synaptic transmission and the alternation between excitatory and inhibitory postsynaptic potentials (15).

This activity translates into what we call "brain rhythms", which integrate time/frequency variations and "brain waves" that depend on the voltage fluctuations of the spectral content; which are the objective of the study to explore the behavior of the brain (16).

In this order of ideas, the EEG signal can be analyzed in the frequency domain, and five main bands of presentation are commonly distinguished —delta, theta, alpha, beta, and gamma (10)—, determined by the speed or slowness of presentation of each one, measured in cycles per second or Hertz (Hz); Gamma waves being the fastest (more than 30 Hz); and the Delta, the slowest (less than 4 Hz) (13); and, logically, the amplitude is inversely proportional to the frequency.

Each of these rhythms has been associated with specific cognitive states, as can be seen in Table 1.

In this line, several studies venture into the neurophysiological, cognitive, and even neuroanatomical identification of the so-called brain waves and their modification through NF training. For example, Wang et al. (17) showed that training through NF of a specific wave, such as Theta (θ), in the 4-8 Hz frequency band, in the anatomical part of the mid-frontal line, could improve the performance of attention and working memory in healthy adults. Likewise, benefits were also verified in the executive function in the younger population.

Non-Invasive Brain Stimulation with NF in Patients with MCI

Based on the previous route (Table 1), brain patterns that fluctuate together with certain reciprocity between the cognitive and behavioral domains have been verified (7). This is how, these non-invasive brain stimulation techniques such as NF, it has been extrapolated and applied to all types of clinical and non-clinical populations, ranging from psychiatric diseases, and neurodevelopmental disorders, to recent studies in elderly people with and without cognitive impairment, this population being a focus of great clinical and research interest, in an attempt to prevent progression to stages of major cognitive impairment (18).

In line with the above, studies have indicated that NF can be a favorable tool in research on neuronal functioning and synchrony with cognitive processes in patients with MCI (19, 20). This is because the NF could generate tools that incite to increase/recover activity in affected brain regions and help them learn to mediate the activation of specific brain regions (21).

MCI has been described, according to multiple investigations, as an intermediate stage between normal aging and what would be the subsequent development of the initial phases of dementia. This includes patients with problems in higher mental functions of a variable degree, depending on the type of dementia. MCI, but without functional impact on activities of daily living (22). This is the differentiating criterion between a minor and a major neurocognitive disorder, according to the latest conceptualization issued by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (23).

The effectiveness of this technique in MCI has been reported in recent clinical studies, which describe that training protocols with NF show a significant increase in brain activity within each training session used in this group of patients. This suggests that the aging brain can still be trained (24). This would indicate, in turn, that NF stimulation could improve the neurocognitive functions of patients with MCI and dementia (25), as in Alzheimer's disease (AD) (26), providing a novel tool to examine the degree, the progression, and improvement of these neurodegenerative pathologies (27). However, the recommendations suggest strengthening the experiments, to generate greater causal relationships or more conclusive results (28).

However, despite the research with results on the efficacy of Neurofeedback in MCI, there is also a gap in the sustainability of rehabilitation, since they work for short periods, non-randomized times. In addition, there are few studies regarding feedback transfer beyond training (24). Not to mention, studies evaluating the efficacy of NF training in this population are still relatively few (3).

For all the above, this review tries to delve into studies on the national and international scene, on the research of training with NF in the performance of physiological notions, combined with effects in the cognitive sphere in patients with MCI.

METHOD

A bibliographic review of scientific articles published in different databases (Science Direct, Web of Science (WoS), Scopus, PubMed/MedLine) was carried out, taking into account publications from 2010 to 2020, using the keywords in English "mild cognitive impairment", "mild cognitive decline", "cognitive disorder", "Neurofeedback", "biofeedback", "brain ware", "EEG feedback" and "Neurofeedback training", and limiting your search to only studies in that language. With the use of Boolean intercession operators (AND and AND) and logical addition (OR and OR), arriving at the following search algorithm: Neurofeedback OR brainwaves OR EEG feedback OR biofeedback AND "mild cognitive impairment" OR cognitive disorder OR MCI.

Criteria for Inclusion and Selection of Articles

To be included, the studies had the following selection parameters: 1. Works derived from a research process; 2. Research variables related to brainwave training with Neurofeedback; 3. That the research studies be with MCI patients; 4. In free access. Once the criteria were applied, 6 articles were finally identified and reviewed that related to the research variables treated in this study (Figure 1).

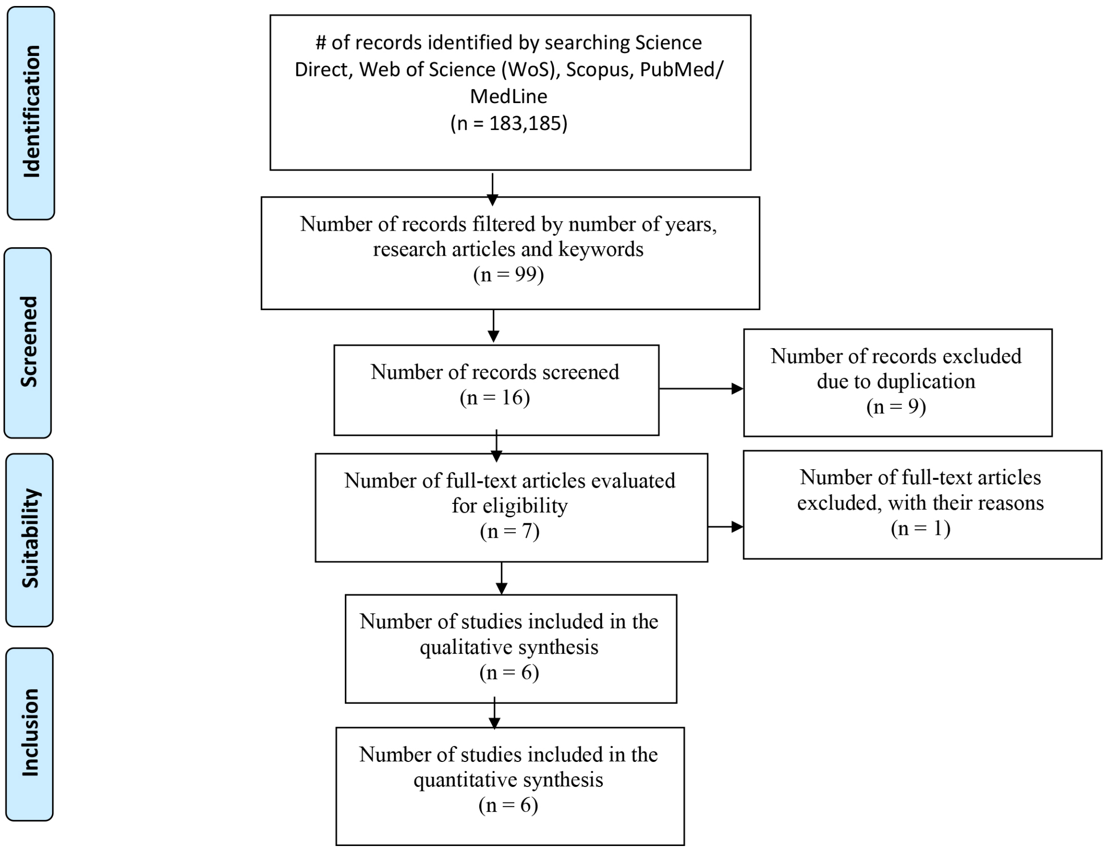

Figure 1. The PRISMA17 statement was followed to report the items in this review.

Results (Table 1) Scientific Articles by Year of Publication (Table 2)

During the review, studies are denoted that start with intensity in 2011 with experimentation in rehabilitation with NF in MCI, associated with neoplasms or other pathologies that compromise the central nervous system (29). After that year, most studies focused on rehabilitation with NF in young adults, trying to enhance cognitive functions through brain wave modification (11,21,30,31). Starting in 2018, research began to appear —mostly clinical trials— aimed at the use of NF and its efficacy in MCI. And, in that sequence, in 2019 and 2020, this type of research registered in the PubMed and Scopus databases increased significantly (Figure 2).

Table 1. EEG Frequency Bands and relationship with Cognitive Status

Brain Rhythm	**Frequency**	**Cognitive Function**	**Brain Area**
Gama	Above 30 Hz (13,44).	They are associated with the condition of consciousness processing, perceptual integration tasks, working memory, and visual and auditory memorization (45-46), and are also involved in visuomotor exercise tasks and sensory-motor attention (47).	Medial frontal parietal cortex (45), and sensorimotor (47-48).
Beta	15-30 Hz (49).	In addition to the sensorimotor area, beta oscillations play other important roles in pure sensory domains such as the modulation of somatosensory input (50) and participation in autonomic nervous system (ANS) functions (49). Beta oscillation can thus be seen as a dynamic biomarker involving somatomotor control and regulation of SNA signals (49).	Motor cortex networks (50). It further serves as a functional link between different brain regions such as the premotor motor and somatosensory cortex, the supplementary motor area, and the cerebellum (49).
Alfa	8-12 Hz (52).	They call the spontaneous activity of the brain in the relaxed state of closed eyes, it is the dominant rhythm in the EEG and is generally associated with a state of relaxation and self-awareness (10), or as a kind of relaxed attention (1). High alpha activity can be observed in regions that are not involved in the current task (7). Subsequently, their training has been found to show positive implications for working memory (53). These oscillations can be considered as a marker of cortical inactivity or an index of active inhibition of sensory information (51).	Thalamic and cortical generators and later the deep layers of the sensory cortices, meaning that the large amplitude of the alpha rhythm would be the result of a coherent cortical input from the thalamus that coincides with the lack of other sensory input, although the mechanisms of the interaction remain unclear(54).
Tetha	de 4-8 Hz (55).	Depending on where in the brain the Theta oscillations are observed, they may be associated with internal orientation, intuition, sleepy states, or memory function (10). Regularly these oscillations can be divided into two groups of hippocampal and cortical theta rhythms. The latter have been related to the encoding, retention, and retrieval of items in working memory (55). On the other hand, depending on its source, it is implicit in variations of functions such as temporary sites for encoding, maintenance, and recovery functions, at the frontal level in task demands, and with more intensity in the same area with memory tasks of work (7), and at the medial frontal level care (17).	It is modulated by different regions of the brainstem, including the nucleus incertus (NI), located in the dorsal tegmentum (49). In addition to showing a clear intracranial peak of the hippocampus (55). Cortical Tetha manifests in temporal and frontal sites, the increase or decrease of which is beneficial for successful memory retrieval (7).
Delta	2–4 Hz(14).	It is implicated in response optimization for task-relevant events and shorter reaction times and attentional selection (56). Next, in Gamma band coupling, they form significant predictors of the multiple unit activity (MUA) response (14).	Primary visual cortex (14, 56-57).

Note: This table shows the frequency bands and their role against a cognitive process and production brain region.

Table 2. Systematization of the Search for Scientific Articles.

Nº	Authors	Year	Research Name	Target	Intervention Protocol	Brain Wave	Cognitive Process	Neurofeedback Equipment	Data Base
1	Jirayucharoensak, Israsena, Panngum, Hemrungrojn, & Maes	2019	A game-based Neurofeedback training system to enhance cognitive performance in healthy elderly subjects and pa-tients with amnestic	Examines the clinical efficacy of a Neurofeedback training system to improve cognitive performance in patients with amnesic mild cognitive impairment (amci) and healthy elderly subjects.	20 sessions of 30 minutes each, 2-3 sessions per week	Beta and al-pha at the level of AF3, AF4, O1, and O2	Cognitive Performance - Working Memory- Sustained Attention	"Emotiv EPOC"	Scopus- WOS- PubMed
2	Marlats, Djabelkhir-Jemmi, Azabou, Boubaya, Pouwels & Rigaud	2019	Comparison of effects between SMR/delta ratio and beta1/ theta-ratio Neurofeed-back Training for older adults with Mild Cognitive Impairment: a protocol for a Randomized controlled trial	To examine whether NF training decreases cognitive impairments, such as memory, attention, and brain electrical activity in elderly people with MCI	30 sessions of 45 minutes each, 2-3 sessions per week	SMR-Delta/ at Cz level and Beta-tetha at the Fz level	Cognitive Performance- Attention	EEG Digitrack Biofeedback plus, Elmiko Inc	SScopus- WOS- PubMed
3	Lavy, Dwolatzk Kaplan, Guez & Todder.	2019	Neurofeedback Improves Memory and Peak Alpha Frequency in Individuals with Mild Cognitive Impairment	I explore the benefits of Neurofeedback for subjects with MCI	10 sessions of 30 minutes each, 5 sessions per week	Upper Alpha to Pz level	Memory, FE, and visuospatial abilities.	Deymed Truscan Acquisition Device, wineeg software	Scopus- WOS- PubMed
4	Jang, Kim, Park, Kim, Jung, Cha, Kim, Kim, Lee, &Yoo.	2019	Beta wave enhancement Neu-rofeedback improves cognitive functions in patients with mild cognitive impairment: A preliminary pilot study	I investigate cognitive enhancement and hemo-dynamic changes in the prefrontal cortex (PFC) after NF Training in MCI patients.	16 sessions of 45 minutes each, 2 sessions per week	Beta in dorsolateral prefrontal cortex	Composite memory, cognitive flexibility, attention, reaction time, and executive function	Procomp Infiniti System, Thought Technology	Scopus-PubMed
5	Marlats, Bao, Chevallie, Boubaya, Djabelkhir-Jemmi, Wu, Lenoir, Rigaud & Azabou.	2020	SMR/Theta Neu-rofeedback Train-ing Improves Cognitive Perfor-mance and EEG Activity in Elderly With Mild Cogni-tive Impairment: A Pilot Study	I examine whether Sen-sorimotor Training (SMR)/ Theta Neurofeedback improves cognitive performance and brain electrical activity in elderly patients with MCI.	20 sessions of 45 minutes each, 2 sessions per week	SMR/Tetha at CZ level	Cognitive Performance - Working Memory and Consolidation	EEG Digitrack Biofeedback plus, Elmiko Inc	Scopus- WOS- PubMed
6	Li, Zhang, Li, Cui & Su.	2020	Neurofeedback Training for Brain Functional Con-nectivity Improvement in Mild Cognitive Impairment	I explore the effectiveness of Neurofeedback to improve functional brain connectivity in patients with mild cognitive impairment	10 sessions, 5 sessions per week, duration until the end of the session (no limit)	Delta, theta, alpha, and beta at connection points Fp1-F3, F3-C3, C3-P3, P3-O1, and Fp2-F4.	Cognitive Performance and Functional Connectivity	NT9200, Beijing Zhongke Xintuo Instrument	Scopus- WOS

Note: The table illustrates the distribution of results by articles.

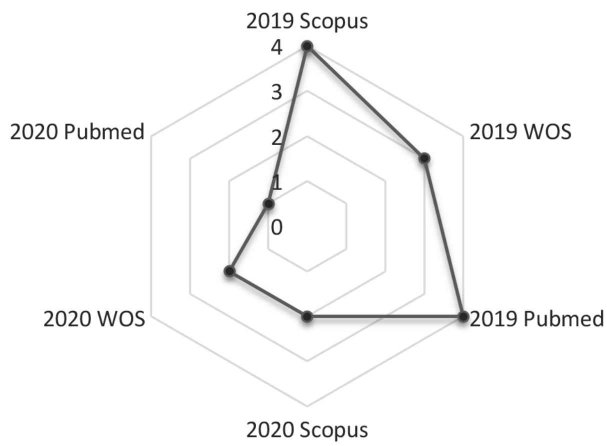

Figure 2. Characterization by Year and Database.
Note: The radial graph shows the proportion of articles in relation to the years and database.

Scientific Articles by Schooling/Years/Sample

A description of the general sociodemographic aspect of the selected articles is presented. In this way, in the first place, it is detailed that the population of these studies had a disparity in the number of subjects that made up their sample, finding from 119 subjects to the incorporation of 5 subjects as the total sample. Next, the vast majority of the studies included a range of 66 years and 6 years of schooling as a mean age. However, no homogeneity was found in demographic characteristics when comparing each article, as shown in Figure 3.

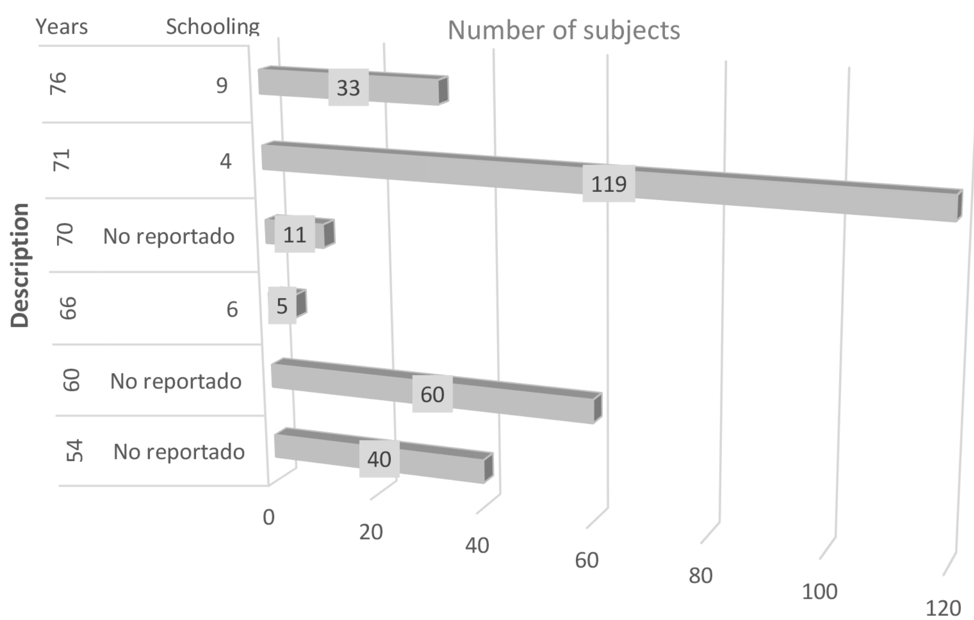

Figure 3. Description by years, schooling, and sample number of articles.
Note: The bar graph shows the description of the articles in relation to the sample, their age, and education.

Distribution by Gender

In the description by gender, it was found in particular that 66 % of the investigations included both genders in their sample. However, it is detailed that 33 % of this percentage included a greater number of women in relation to men. Likewise, 50 % of the studies carried out specify the female gender as the greatest denominator when carrying out studies on individuals with MCI.

Next, a small percentage (17 %) was found that did not specify gender in the selected sample, and in an equal percentage (17 %) studies were found that included only one gender: female.

Neurofeedback Training Protocol

In the review of the intervention protocol, it was found that 60 % of the investigations incorporated an intensity of 45 minutes per session, followed by 30 minutes with 40 %, finding only one article that did not include a training limit within its protocol.

Similarly, the sessions included a number of 2 to 5 sessions per week, where the highest percentage was located with the realization of 2 and 3 sessions during the week with 90 %, finding only a single antecedent represented in 10 %, which included intensity of 5 weekly sessions, one per day.

Regarding the number of total sessions, these studies varied with a total intensity of 10 sessions (40 %), 20 sessions (40 %), and, to a lesser extent, studies with 30 and 16 total sessions, V with a percentage of 10 % for each (Figure 4).

Characterization of Wave, Connection, and Cognitive Process

When analyzing the distribution, it is found that there is no similarity in the protocol used by these studies, observing that in the different articles there is no evidence of a standard pattern of experimentation, in terms of location of brain activity recording, stimulation time, and frequency. All of the studies examine the frontal, central, parietal, and occipital cortex. No studies on the temporal cortex were found.

In agreement, at the level of stimulation of processes or cognitive domains, we evidence different processes anchored to each intervention protocol, highlighting memory as the most evaluated, in its different clinical and neuropsychological dimensions, followed by attention and executive functions (Table 3).

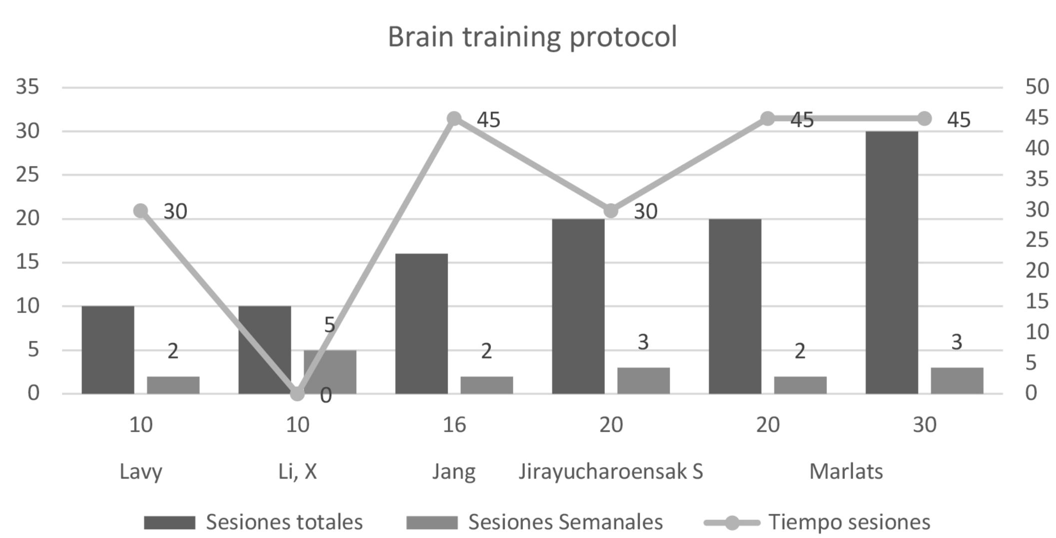

Figure 4. Description of the training protocol by author
Note: The bar graph illustrates the variety of training protocols by the author.

Table 3. Description of Connection Protocol, Brain Wave, and Cognitive Process

Connection	Brain Wave	Proceso Cognitivo
CZ	SMR / Theta	Cognitive Performance - Working Memory
F3, F4, O1 y O2	Beta-Alfa	Cognitive Performance - Work-ing Memory - Sustained Attention
CZ /FZ	SMR-Delta/ Beta-Theta	Cognitive Performance- Attention
Fp1-F3, F3-C3, C3-P3, P3-O1, y Fp2-F4)	Delta, Theta, Alfa Y Beta	Functional Connectivity
Pz	Alfa Superior	Memory, FE, and Visuospatial Abilities.
PF	Beta	Composite Memory, Cognitive Flexibility, Attention, Reaction Time, and Executive Function

Note: The table details the variety of connection protocols, brain waves, and cognitive processes that were found as a result of the review.

DISCUSSION

Regarding the discussion variables, it was found —based on the research review— the growing interest in MCI as a prodromal stage of a dementing process and, more linearly, with AD (2). It is for this reason that some authors (32) describe the level of incidence and the high associative risk of patients with this pathological condition against the development of this disease. In addition to reporting a rapid rate of decline in cognitive function, compared to people who do not have any clinical signs of MCI.

In this way, just as the importance of MCI has been reported as a focus of interest for the scientific community, the need for prevention is also contiguous with the development of AD. However, it is prudent to mention that, although MCI is usually evoked as a transitional stage to a dementing process, there are authors who highlight in their studies that the condition and the conversion rates remain controversial (33). This is how we find annual conversion rates of 10 to 30 % and 20 to 66 % (34), as well as others that highlight approximately 15 % (35). And, if we add to this the scarce pharmacological evidence that contributes to this conversion rate, the need to continue delving into studies with non-invasive stimulation techniques is highlighted, for their use as a treatment option.

In recent years, emphasis has been placed on different intervention models for MCI: pharmacological, genetic, epigenetic, and neurophysiological. In any case, studies on this pathology —mainly in the line of intervention through Neurofeedback— go back with greater intensity in recent years (36-39), positioning it as an important technique for self-regulation of brain activity and cognitive potential in these patients (40,41).

This is how, through the review of the effectiveness as an intervention technique, all the antecedents coincide in expressing the clinical employability that it has in patients with MCI (3,37-40), especially in potential therapeutic applications to prevent the progression of MCI to major cognitive impairment (25).

Therefore, when referring to brainwave training in MCI through NF neurofeedback, the review showed differences in the implementation of specific activation/inhibition protocols in different frequency bands, as well as the cognitive process that is desired to impact.

This finding, in the variety of intervention protocols, is parallel to various investigations that through their experimentation have contributed to the field of connectivity and functional intensity in MCI. For example, one study showed a correlation between cognitive decline and decreased gamma activity (24). Likewise, it has been found that patients with MCI show an increase in Theta power and a decrease in Beta power, while patients with advanced dementia show a decrease in Alpha power and an increase in Delta power (20). On the other hand, other authors show discrepancies in these results, finding, for their part, that both MCI and EA share the same pattern of EEG activation related to working memory characterized by an increase in P200-N200 latencies and a decrease of Beta power (42). Finally, other authors report theta wave overactivity in dementia studies, compared to normal older people (26). Consequently, other authors suggest low functional connectivity in patients with MCI, mainly in the Beta rhythm (3,29).

This demonstrates the need for further research in this field. Above all, in order to standardize intervention protocols (frequency, intensity, recording location, among others), which allow demonstrating the probable efficacy of these non-invasive models and intervention for prevention, early intervention and timely rehabilitation for individuals with this pathology.

Finally, it is worth highlighting the importance of gender when defining intervention models with Neurofeedback in MCI, considering the difference in functional connectivity between male and female genders, especially in the sensory-motor network (SMN), the dorsal attention network, and the relationship with the white matter, which in women tend to be more affected in this population (43). For this reason, taking into account the findings of this review, where the studies showed a greater population inclination towards the female sex, it should be considered a relevant factor when establishing differences in MCI progress.

Based on all of the above, the present investigation sought to carry out a characterization through a review of Neurofeedback training and how, through it, some physiological and cognitive notions can be improved in patients with MCI, in addition to its most notorious generalities. That is why some of the conclusions and reflections that stand out from this study are:

- Intervention with NF as an intervention tool, which shows probable efficacy in both the research and clinical fields: promising results.
- The brain —even in normal aging or in MCI— shows learning and a good training response through neurofeedback by NF, being able to increase the modeling of frequency bands and increase functional connectivity, potentially impacting cognitive function in people with MCI, allowing them to benefit brain reserve.
- To date, various training protocols, connections, and training times can be seen, not be possible to single or similar reference when conducting research in the line of rehabilitation with NF in patients with MCI.
- The importance of establishing a homogeneous distribution in terms of gender is made clear when consolidating the sample.
- Finally, more neurophysiological rehabilitation studies are encouraged with the use of non-invasive techniques such as NF, which feed knowledge on EEG frequency band waves, brain connections, and cognitive function.

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